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10/580,563	05/26/2006	Susanne Matheus	MERCK-3169	5970

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EXAMINER	
NOAKES, SUZANNE MARIE	
ART UNIT	PAPER NUMBER
1656	

NOTIFICATION DATE	DELIVERY MODE
08/05/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docketing@mwzb.com

Office Action Summary	Application No.	Applicant(s)	
	10/580,563	MATHEUS ET AL.	
	Examiner	Art Unit	
	SUZANNE M. NOAKES	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 March 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,9-13,17,18 and 22* is/are pending in the application.

4a) Of the above claim(s) *17 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,9-13 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 17 March 2010 has been entered.

Status of the Claims

2. The amendments filed 17 March 2010 are acknowledged. Applicants have canceled claim 8 and 21; thus, claims 1-3, 9-13, 17, 18, 21 and 22 are pending and claims 17 and 18 remain withdrawn from further consideration for being drawn to non-elected subject matter. Claims 1-3, 9-13 and 22 are subject to examination on the merits.

Withdrawal of Rejections/Objections

3. Any rejection/objection recited in the previous Office action and not explicitly restated below is hereby withdrawn.

4. The rejection of claims 1-3, 8-13, 21 and 22 are rejected under 35 U.S.C. 112, first paragraph, enablement (Biological Deposits statement) is withdrawn in view of Applicants response and Exhibits A & B.

5. The rejection of claims 1-3, 8-13, 21 and 22 under 35 USC 112 1st paragraph, written description is withdrawn in view of the amendments to the claims.

Maintained Rejections/Objections

Claim Rejections - 35 USC § 112 – 1st paragraph

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-3, 9-13 and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for solid crystals of whole murine humanized monoclonal antibodies of Erbitux™/MabC225/Cetuximab (all synonyms of one another) produced by very specific crystallization methods and conditions of Example 2 and 3 only, does not reasonably provide enablement for crystals of Erbitux™/MabC225/Cetuximab produced under a variety of conditions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are drawn to crystals of cetuximab which are made by precipitating an aqueous solution of said antibodies by means of a precipitating agent. However, the specification *only* sufficiently describes crystals that have been produced by the specific examples described in Examples 2 and 3 which discloses using Erbitux™ at a concentration of 20mg/ml in either 10 mM phosphate buffer at pH 8.0 or 10 mM citrate

buffer at pH 5.5, adding either 10 mM phosphate buffer pH 8.0 to the phosphate protein solution or 10 mM citrate buffer pH 5.5 to the citrate protein solutions, respectively, and finally adding saturated ammonium sulfate in 10 mM phosphate buffer pH 8.0 to the phosphate protein-buffer solution or 50% v/v ethanol in 10 mM citrate buffer pH 5.5 to the citrate protein-buffer solution, respectively (it is noted that all additions are phosphate buffers to phosphate buffers and citrate buffers to citrate buffers/salts) and shaking this solution by hand for an undisclosed period of time at either room temperature or 4°C. It is presumed that the anti-EGFR antibody humanized monoclonal antibody Erbitux™ used in the crystallization procedures of Examples 2 and 3 is commercially purchased but this is not disclosed. Beyond this scope, however, the specification and claims are not sufficiently enabled for a skilled artisan not to have to endure a considerable amount of undue experimentation because there is considerably unpredictability in crystallizing any protein or antibody to begin. Furthermore, the specification states that this is the first time any anti-EGFR antibody has been crystallized, especially, Erbitux/MabC225/Cetuximab and thus there is no prior art teachings a skilled artisan can rely upon for help or guidance beyond the prior art of Li et al. (cited previously) which falls between the foreign priority date and the effective filing date of the instant PCT. Thus, a skilled artisan, in order to achieve the full scope of that which is being claimed, would be required to practice undue experimentation. In this case, the burden is seen as undue when the Wands analysis is considered.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

In the instant case, the quantity of experimentation would be considerable because the smallest change in ***any*** parameter in crystallizing a protein/antibody can have enormous consequences. Thus, it is not enough to have the crystallization conditions of a related/similar protein/antibody or 'native' protein/antibody. Rather, what would be required is the disclosure of the precipitating reagents as claimed.

The nature of the invention and of the prior art suggests that crystallizing proteins and antibodies is an extremely tenuous science; what works for one protein or antibody does not necessarily for another, and what works for one native protein or antibody

does not necessarily work for a mutant or fragment or variant (even those with conserved substitutions) even though they essentially contain the same protein/antibody that has already been crystallized. It is noted that Applicants attempted to crystallize Erbitux™ using a commercially available crystallization grid matrix screen, Crystal Wizard I, and were only able to successfully produce salt crystals (see Example 8). Thus, this also lends weight to the fact that crystallization of proteins and antibodies is not straight forward and is unpredictable at best. Specific overexpression protocols, precise protein purification protocols and exact crystallization conditions (e.g. temperature, buffer, salt, protein concentration etc.) are needed for each protein and/or antibody (see Weber, Overview of Crystallization Methods. Methods in Enzymology, 1997, Vol. 276, pp. 13-22).

The nature of the invention and of the prior art suggests that crystallizing proteins is an extremely tenuous science; what works for one protein does not necessarily for another, and what works for one native protein does not necessarily work for a mutant or a protein complex even though they contain the same protein that has already been crystallized. Specific crystallization conditions (e.g. temperature, buffer, salt, protein concentration etc.) are needed for each protein (or protein complex). McPherson (Eur. J. Biochem. 1990, 189:1-23) outlines 25 different parameters which do or could affect the crystallization of any protein (see Table 2, p. 13). It is stated (p. 13, 2nd column, *Factors influencing protein crystal growth*):

> "Table 2 lists physical, chemical and biological variables that may influence to a greater or lesser extent the crystallization of proteins. The difficulty in properly arriving at a just assignment of importance for each factor is substantial for several reasons. Every protein is different in its properties and, surprisingly perhaps, this applies even to proteins that differ by

> no more than one or just a few amino acids. There are even cases where the identical protein prepared by different procedures or at different times may show significant variations. In addition, each factor may differ considerably in importance for individual proteins."

Thus, each protein that is to be crystallized needs to be treated as its own entity possessing its own unique biochemical crystallization parameters which cannot be inferred or learned from other crystallized proteins, even those having only one or two substitutions compared to the "wild-type" crystallized protein.

Even when assisted by the latest technologies such as automated robotics, the art of crystallography is still rooted in trial-and-error procedures (see Abstract, Kundrot et al. Cell. Mol. Life Sci. 2004, 61: 525-536 and Benevenuti et al., Nature Protocols, published on-line 28 June 2007, 2(7):1633-1651) and currently there are no directed methods which makes this process any easier. Thus, even those that are skilled in the art at a very high level which have the added benefit of the latest technology fair no better in successfully crystallizing proteins of interest. In addition to the trial-and-error approaches mandated by this particular science, one of the best known unexplained facilitators in successful crystallization is simply just luck. This aspect of protein crystallography is very well known in the art; see for example, "Protein Crystallization and Dumb Luck" by R. Cudney, Rigaku Journal, 1999, Vol. 16, No. 1, pp. 1-7; and Drenth, "Principles of Protein X-Ray Crystallography", 2nd Edition, 1999 Springer-Verlag New York Inc., Chapter 1, p. 19, 4th paragraph, lines 1-2.

Finally it is noted that all of this specifically and unequivocally applies to antibodies and monoclonal antibodies which have proved difficult to crystallize. It is noted that c225 is a chimeric monoclonal antibody and Ahamed et al. (2007,

Biochemical J., Vol. 93, pp.610-619) state the following regarding monoclonal antibody crystallization (see pp. 610, last paragraph to p. 611).

> Monoclonal antibodies (MAbs) are flexible macromolecules that can assume a wide range of conformations as a consequence of their intrinsic domain mobility and segmental flexibility. MAbs have recently been recognized as enormously efficacious therapeutics, which can be applied to treat numerous life-threatening disease, including cancer and immune diseases. MAbs are also well established as specific serologic reagents for a number of immunoassays and diagnostics for the detection of a wide variety of antigens thanks to either unlimited availability (11). *Unfortunately, MAbs are extremely difficult to crystallize as intact molecules, probably because of their structural complexity and variability. Most of the published MAb crystallization experiments have been restricted to either Fab-antigen complexes or MAb fragments of MAbs without a hinge region. Nevertheless, successful crystallization of intact MAbs has been reported on several occasions (10, 12-16). However, successful crystallization of one MAb obviously does not imply that other MAbs will equally readily crystallize under the same solution conditions.*

Furthermore, the prior art is of little assistance because while other MAbs might have been crystallized previously, the conditions are likely wholly irrelevant here. Thus, when all things are considered and the Wands factors are treated on their merits, the claim is not enabled because a great deal of undue experimentation would be expected and necessary in order to practice the full scope of claimed invention.

Therefore, claims to cetuximab made by the claimed broad product by process, are not fully enabled beyond that described in Examples 2 and 3 for the whole murine humanized monoclonal antibody of Erbitux/MabC225/cetuximab.

Applicants Remarks and Examiner's Rebuttal:

Applicants remarks have been considered but are not found persuasive regarding the enablement as noted in the rejection above for claims 1-3, 9-13 and 22.

Applicants specifically state that Example 2 provides a disclosure of crystallization of Erbitux with ammonium sulfate. Example 3 relates to another embodiment, wherein crystallization of Erbitux with ethanol is provided. See, pages 46-47 of the specification. Methods for visually and/or spectroscopically characterizing the crystals of the present invention (for example, with respect to size and or IR spectra) are also provided. See, Examples 6-7 at page 49 of the specification. And that is the Examiner's burden to establish a definitive case for undue experimentation. It is alleged the previous rejection did not satisfy this requirement. Applicants specifically state the supporting references of Weber et al. (Methods in Enzymology, 1997), MacPherson et al. (Journal of Biochemistry, 1990) and Drenth et al. (Principles of X- ray crystallography, 1st edition: 1990) to support the contention that protein crystallization is unpredictable are unsatisfactory because MacPherson is fully thirteen years before the earliest priority date of the instant application, and as such, fails to appreciate the progress made in the field of X- ray crystallography during this period. MacPherson further provides an overview of challenges associated with crystallization of large macromolecules, including, viruses, polynucleotides, and the like. Although not much specific guidance as to crystallization of antibody molecules, in Fig. 6, the reference teaches that crystals of albumin can be obtained. Drenth generically teaches that it is difficult to predict conditions for growing protein crystals, but fails to provide any specific guidance on the crystallization of globular (i.e., water-soluble) proteins, such as antibody molecules. It is art appreciated, for example, that transmembrane (i.e., integral) proteins are more difficult to crystallize than globular proteins (due to, for

example, difficulties in expression, difficulties in solubilization, and difficulties in crystallization). Globular and cytosolic proteins face fewer challenges. Anti-tumor antibody molecules, and particularly the Fab portions that bind to antigens of interest, have been crystallized at high resolutions (see, Harris et al. "The three-dimensional structure of an intact monoclonal antibody for canine lymphoma" Nature, 36o(64o2):369-72,1992).

While the examiner does not concede that these references are unsatisfactory, and instead asserts that the age of the references or the general guidance provided therein is still as applicable today as the day they were published and further that the general guidance applies as applicably to antibodies as it does proteins or enzymes in generally, the Examiner has provided additional references to support these assertions and the conclusions which the Examiner has arrived. Applicants are specifically and emphatically referred to Ahamed et al. as cited above as well as Kundrot et al, Cudney and Beneveunti et al. (also cited above). As such, there is an expectatation of under search burdens upon those skilled in the art, even those with automated assistance, in trying to ascertain the crystallization conditions necessary for the chimeric monoclonal antibody c225.

Conclusion

8. No claim is allowed 1-3, 9-13 and 22 are rejected.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUZANNE M. NOAKES whose telephone number is (571)272-2924. The examiner can normally be reached on 7.00 AM-3.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Suzanne M. Noakes/
Primary Examiner, Art Unit 1656
29 July 2010